METHODS OF REDUCING POLYSORBATE DEGRADATION IN DRUG FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/982,346, filed Feb. 27, 2020, U.S. Provisional Patent Application No. 63/021,181, filed May 7, 2020 and U.S. Provisional Patent Application No. 63/073,125, filed Sep. 1, 2020, the contents of which are incorporated herein by reference in their entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 18, 2021, is named 070816-01942_SL.txt and is 20,608 bytes in size.

FIELD

[0003] The present invention generally pertains to compositions with reduced amount of certain lipases, methods of making such compositions and methods of reducing polysorbate degradation due to the presence of such lipases. In particular, the present invention generally pertains to compositions and methods of making compositions with reduced presence of liver carboxylesterase-B 1-like protein and liver carboxylesterase-1-like protein.

BACKGROUND

[0004] Among drug products, protein-based biotherapeutics are an important class of drugs that offer a high level of selectivity, potency and efficacy, as evidenced by the considerable increase in clinical trials with monoclonal antibodies (mAbs) over the past several years. Bringing a protein-based biotherapeutic to the clinic can be a multiyear undertaking requiring coordinated efforts throughout various research and development disciplines, including discovery, process and formulation development, analytical characterization, and pre-clinical toxicology and pharmacology.

[0005] One critical aspect for a clinically and commercially viable biotherapeutic is stability of the drug product in terms of the manufacturing process as well as shelf life. This often necessitates appropriate steps to help increase physical and chemical stability of the protein-based biotherapeutics throughout the different solution conditions and environments necessary for manufacturing and storage with minimal impact on product quality, including identifying molecules with greater inherent stability, protein engineering, and formulation development. Surfactants, such as, polysorbate are often used to enhance the physical stability of a protein-based biotherapeutic product. Over seventy percent of marketed monoclonal antibody therapeutics contain between 0.001% and 0.1% polysorbate, a type of surfactant, to impart physical stability to the protein-based biotherapeutics. Polysorbates are susceptible to auto-oxidation and hydrolysis, which results in free fatty acids and subsequent fatty acid particle formation. The degradation of polysorbate can adversely affect the drug product quality since polysorbate can protect against interfacial stress, such as aggregation and adsorption. Presence of some lipases can be a likely cause of degradation of polysorbates in a formulation. Thus, such lipases in drug products need to be detected, monitored and reduced.

[0006] Direct analysis of lipases can require isolation of the product in a sufficiently large amount for the assay, which is undesirable and has only been possible in selected cases. Hence, it is a challenging task to determine the workflow and analytical tests required to characterize lipases responsible for polysorbate degradation in a sample. In addition to detecting the lipases responsible for polysorbate degradation, the drug product must be obtained by purification methods that remove or reduce such lipases.

[0007] It will be appreciated that a need exists for methods for depleting lipase from a formulated drug product.

SUMMARY

[0008] Maintaining stability of drug formulations, not only during storage but also during manufacturing, shipment, handling and administration, is a significant challenge. Among drug products, protein biotherapeutics are gaining popularity due to their success and versatility. One of the major challenges for protein biotherapeutics development is to overcome the limited stability of the protein and excipients in the products, which can be affected by the presence of lipases (present as host-cell proteins). Evaluation of its effect on the drug formulation and reduction of such lipases can be an important step in drug formulation development, followed by methods to prepare the drug formulation so as to have reduced lipases and increased stability owing to the reduced lipases.

[0009] In one exemplary embodiment, the disclosure provides a method of depleting lipase from a sample comprising contacting the sample including lipase with a probe, said probe capable of binding to the lipase to form a complex and separating the complex from the sample to thereby deplete the lipase from the sample. In one aspect, the sample can comprise a protein of interest. In one aspect, the sample can comprise a polysorbate excipient. In a specific aspect, the polysorbate excipient can be selected from polysorbate-20, polysorbate-60, polysorbate-80 or combinations thereof. In yet another specific aspect, the polysorbate excipient is polysorbate-80.

[0010] In one aspect, the lipase is liver carboxylesterase-B1-like protein. In another aspect, the lipase is liver carboxylesterase-1-like protein.

[0011] In one aspect, the lipase is capable of degrading the polysorbate in the sample. Thus, the method of this embodiment reduces the degradation of polysorbates by depleting the sample of the lipase.

[0012] In one aspect, the probe can be capable of being linked to a solid support. In a specific aspect, the solid support can be agarose beads or magnetic beads.

[0013] In one aspect, the probe can be attached to a solid support using a ligand. In a specific aspect, the ligand can be an indicator, biotin molecule, a modified biotin molecule, a nuclei, a sequence, an epitope tag, an electron poor molecule or an electron rich molecule.

[0014] In one aspect, the method can further comprise recovering the lipase from the complex.

[0015] In one exemplary embodiment, the disclosure provides a method of purifying a sample having a protein of interest and a lipase, comprising contacting the sample with a probe, said probe capable of binding to the lipase to form a complex and separating the complex from the sample. In